Tislelizumab (TIS) Plus Chemotherapy (Chemo) vs Placebo (PBO) Plus Chemo as First-Line (1L) Treatment of Advanced Gastric or Gastroesophageal Junction Adenocarcinoma (GC/GEJC): Health-Related Quality of Life (HRQoL) Outcomes in the RATIONALE-305 Study

Marcia Cruz Correa,[1*] Rui-Hua Xu,[2] Markus Moehler,[3] Do-Youn Oh,[4] Ken Kato,[5] David Spigel,[6] Hendrik-Tobias Arkenau,[7] Josep Tabernero,[8] Anastasia V. Zimina,[9] Yuxian Bai,[10] Jianhua Shi,[11] Keun-Wook Lee,[12] Hidekazu Hirano,[5] Lucjan Wyrwicz,[13] Roberto Pazo Cid,[14] Hui Xu,[15] Tao Sheng,[16] Gisoo Barnes[16]

*Presenting author

[1]University of Puerto Rico, School of Medicine, San Juan, Puerto Rico; [2]University Cancer Center State Key Laboratory of Oncology in South China, Collaborative Innovation Center of Cancer Medicine, Department of Medical Oncology, Guangzhou, China; [3]Johannes-Gutenberg University Clinic, Department of Internal Medicine I, Mainz, Germany; [4]Seoul National University Hospital Cancer Research Institute, Seoul National University College of Medicine, Department of Internal Medicine, Seoul, Republic of Korea; [5]National Cancer Center Hospital, Department of Gastrointestinal Medical Oncology, Tokyo, Japan; [6]Sarah Cannon Research Institute, Nashville, TN, USA; [7]Sarah Cannon Research, London, UK; [8]Vall d'Hebron University Hospital, Department of Medical Oncology, Barcelona, Spain; [9]BIH of Omsk Region, Clinical Oncology Dispensary, Omsk Oblast, Russia; [10]Harbin Medical University Cancer Hospital, Department of Gastrointestinal Oncology, Harbin, China; [11]Linyi Cancer Hospital, Department II of Medical Oncology, Linyi, China; [12]Seoul National University College of Medicine, Seoul National University Bundang Hospital, Department of Medical Oncology (Internal Medicine), Seongnam, Republic of Korea; [13]Maria Sklodowska-Curie National Cancer Research Institute, Department of Oncology and Radiotherapy, Warsaw, Poland; [14]Hospital Universitario Miguel Servet, Department of Medical Oncology, Zaragoza, Spain; [15]BeiGene (Beijing) Co., Ltd., Beijing, China; [16]BeiGene USA, Inc., San Mateo, CA, USA

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Conclusions

- **Advanced or metastatic GC/GEJC patients had better HRQoL outcomes with tislelizumab plus chemotherapy compared with placebo plus chemotherapy**
- **These better HRQoL outcomes were maintained through Cycles 4 and 6, corresponding to approximately 9 and 15 weeks, respectively**
- **The sustained and improved HRQoL in overall health status, physical functioning, and gastric cancer disease-specific symptoms concurred well with improved efficacy and safety results of tislelizumab plus chemotherapy**
- **Tislelizumab plus chemotherapy can potentially serve as a 1L treatment for advanced or metastatic GC/GEJC patients**

Background

- Gastric cancer, including gastric or gastroesophageal junction adenocarcinoma (GC/GEJC), continues to be one of the most common forms of cancer and a leading cause of cancer death worldwide[1]
- Individuals with gastric cancer commonly experience symptoms such as fatigue, diarrhea, sleep disorders, and eating difficulties[2-4] thus having a detrimental impact on patients' health-related quality of life (HRQoL)
- RATIONALE-305 (NCT03777657), a phase 3 study, examined the efficacy of tislelizumab plus chemotherapy compared with placebo plus chemotherapy in adults with GC/GEJC
  - Tislelizumab plus chemotherapy demonstrated significant improvements in overall survival vs placebo plus chemotherapy in patients with a PD-L1 score ≥5% (median 17.2 months vs 12.6 months; hazard ratio [HR] 0.74, [95% confidence interval (CI) 0.59–0.94]; *P*=0.0056 [at interim analysis]) and in all randomized patients (median 15.0 months vs 12.9 months; HR 0.80 [95% CI 0.70–0.92]; *P*=0.0011 [at final analysis])
  - Grade ≥3 treatment-related adverse events were observed in 54% vs 50% of patients in the tislelizumab plus chemotherapy and placebo plus chemotherapy arms, respectively

Objective

- The purpose of the current analyses was to assess HRQoL in patients treated with tislelizumab or placebo plus chemotherapy in the RATIONALE-305 study

Methods

Study Design and Patients

- RATIONALE-305 was a randomized, open-label, multicenter, multiregional phase 3 study
- The study population consisted of adults (aged ≥18 years) with previously untreated locally advanced unresectable or metastatic GC/GEJC
- Eligible patients were randomized 1:1 to receive tislelizumab 200 mg or placebo intravenously once every 3 weeks plus investigator's choice of chemotherapy regimen until disease progression, unacceptable toxicity, or patient withdrawal
- HRQoL was a secondary endpoint and was assessed using patient-reported outcomes (PROs)

Assessments and Analyses

- The PRO measures were collected at baseline (treatment Cycle 1, Day 1) and then every cycle (each 21-day cycle) for the first 6 cycles and every other cycle thereafter
- Key clinical cycles were Cycles 4 and 6 and were pre-specified as clinically justifiable for assessing the short- and long-term treatment effects in both arms[5-7]
- The following key pre-specified PRO endpoints were selected based on their relevance to gastric cancer and treatment side effects, as well as their use in previous studies:
  - European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire – Core 30 (QLQ-C30): global health status/quality of life (GHS/QoL), physical functioning, and fatigue symptom scales. Higher scores on the GHS/QoL and physical functioning scales indicate better HRQoL or functioning, whereas a higher score on the fatigue symptom scale suggests worse symptoms
  - EORTC Quality of Life Questionnaire – Gastric Cancer Module (QLQ-STO22): symptom index, dysphagia/odynophagia, pain/discomfort, upper gastrointestinal symptoms, and dietary restrictions scales. Higher scores on the QLQ-STO22 indicate worse symptoms or problems
- Higher scores on the GHS/QoL and physical functioning scales and lower scores on symptom scales indicate better outcomes

Statistical Analysis

- All analyses were conducted using the data cut-off of February 28, 2023
- All randomized patients who completed the baseline, and at least one post-baseline PRO questionnaire were included in this analysis
- Adjusted completion rates were defined as the number of patients who completed the questionnaires at each cycle divided by the number still on treatment
- Change from baseline in each key PRO endpoint to Cycle 4 and Cycle 6 was analyzed using a constrained longitudinal data analysis model; differences in the least-squares (LS) mean change (95% CI) from baseline to key clinical cycles of Cycle 4 and Cycle 6 between the arms were assessed. The model included baseline score, stratification factors, treatment arm, visit, and treatment arm by visit interaction as fixed effects and visit as a repeated measure. *P*-values were 2-sided and nominal
  - Between-group comparisons were reported as differences in the LS mean change from baseline with 95% CIs
  - A clinically meaningful change was defined as a 5-point mean change from baseline[8-10]
- Time to deterioration was defined as time to first onset of a ≥10-point change in the worsening direction from baseline with confirmation by a subsequent worsening; the Kaplan-Meier method was used to estimate the deterioration curve in each group
  - The log-rank test and hazard ratios showed the magnitude of treatment effect

Results

- The intent-to-treat population consisted of a total of 997 patients randomized to receive either tislelizumab plus chemotherapy (n=501) or placebo plus chemotherapy (n=496)
- Patient demographics and baseline disease characteristics were generally balanced across treatment arms (**Table 1**)

Adjusted Completion Rates

- The adjusted completion rates were high (>91%) and consistent across treatment arms at each assessment timepoint

Change from Baseline to Cycle 4

- Better outcomes were observed in the tislelizumab plus chemotherapy arm vs the placebo plus chemotherapy arm. The decrease in pain/discomfort of -6.88 (-8.39, -5.36) was clinically meaningful in the tislelizumab plus chemotherapy arm (**Figure 1**)

Change from Baseline to Cycle 6

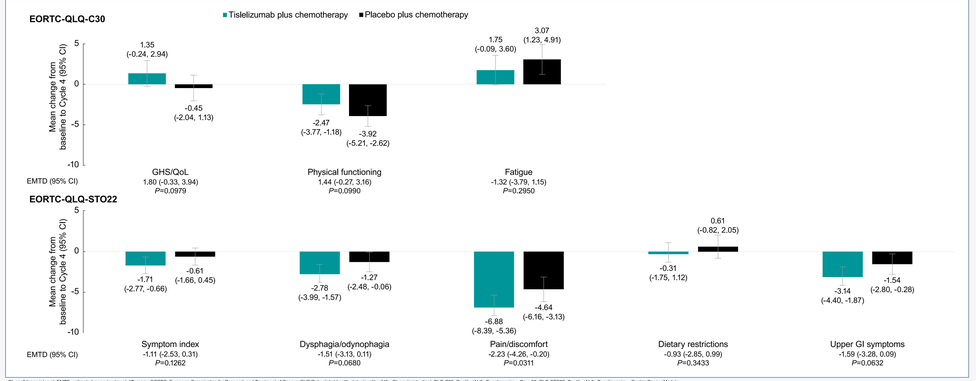
- Better outcomes were observed in the tislelizumab plus chemotherapy arm at Cycle 6 (**Figure 2**)
- The decrease in pain/discomfort continued to be observed in the tislelizumab plus chemotherapy arm, whereas decrease (worsening) of physical functioning was observed in the placebo plus chemotherapy arm

Table 1. Demographics and Baseline Disease Characteristics

	Tislelizumab plus chemotherapy (n=501)	Placebo plus chemotherapy (n=496)
Median age, years (IQR)	60.0 (53.0–66.0)	61.0 (54.0–68.0)
Sex		
Male	346 (69)	346 (70)
Female	155 (31)	150 (30)
Race		
Asian	376 (75)	372 (75)
White	116 (23)	107 (22)
Other*	9 (2)	17 (3)
Geographical region		
Asia	376 (75)	372 (75)
China	259 (52)	257 (52)
Japan and South Korea	117 (23)	115 (23)
North America/Europe	125 (25)	124 (25)
ECOG performance status		
0	169 (34)	154 (31)
1	332 (66)	342 (69)
Primary tumor location		
Stomach	405 (81)	395 (80)
GEJC	96 (19)	100 (20)†
Metastatic disease	494 (99)	490 (99)
Metastatic sites		
0–2	335 (67)	335 (68)
≥3	166 (33)	160 (32)
Liver metastases	190 (38)	188 (38)
Peritoneal metastases	220 (44)	214 (43)
Prior adjuvant/neoadjuvant treatment	107 (21)	100 (20)
Prior gastrectomy/esophagectomy	133 (27)	139 (28)
MSI or MMR status		
MSI-H/dMMR	16 (3)	24 (5)
MSI-L/MSS/pMMR	448 (89)	439 (89)
Unknown	37 (7)	33 (7)
PD-L1 expression score		
<5%	227 (45)	224 (45)
≥5%	274 (55)	272 (55)

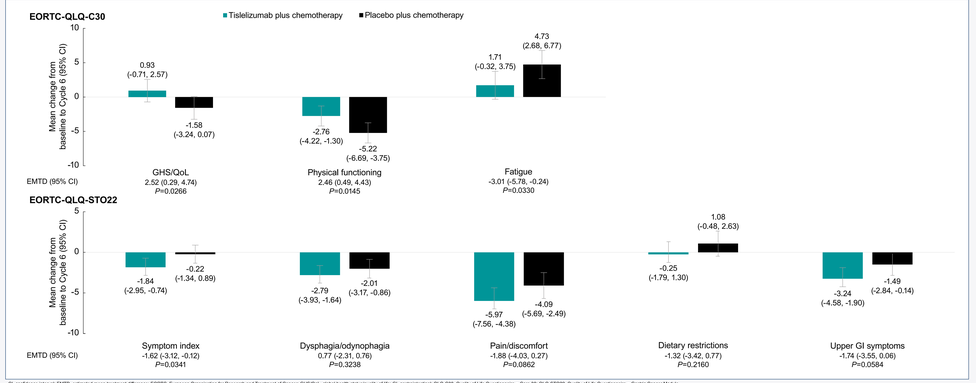
Data cut-off: February 28, 2023. Data are n (%) unless specified otherwise.
*Includes not reported, unknown and other.
†The diagnosis of one patient was updated from gastric adenocarcinoma to pancreatic cancer after randomization.
dMMR, deficient mismatch repair; ECOG, Eastern Cooperative Oncology Group; GEJC, gastroesophageal junction carcinoma; IQR, interquartile range; MSI-H/L, microsatellite instability-high/low; MSS, microsatellite stable; PD-L1, programmed death-ligand 1; pMMR, proficient mismatch repair.

Figure 1. Least-Squares Mean Change from Baseline at Cycle 4 and by Treatment Arm



CI, confidence interval; EMTD, estimated mean treatment difference; EORTC, European Organisation for Research and Treatment of Cancer; GHS/QoL, global health status/quality of life; GI, gastrointestinal; QLQ-C30, Quality of Life Questionnaire – Core 30; QLQ-STO22, Quality of Life Questionnaire – Gastric Cancer Module.

Figure 2. Least-Squares Mean Change from Baseline at Cycle 6 and by Treatment Arm



CI, confidence interval; EMTD, estimated mean treatment difference; EORTC, European Organisation for Research and Treatment of Cancer; GHS/QoL, global health status/quality of life; GI, gastrointestinal; QLQ-C30, Quality of Life Questionnaire – Core 30; QLQ-STO22, Quality of Life Questionnaire – Gastric Cancer Module.

Time to Deterioration

- Results showed patients receiving tislelizumab plus chemotherapy were at a lower risk of deterioration as indicated by GHS/QoL, physical functioning, QLQ-STO22 symptom index, pain/discomfort, and upper gastrointestinal symptoms (**Table 2**)

Table 2. Time to Deterioration for EORTC QLQ-C30 and QLQ-STO22 Scales

		Tislelizumab plus chemotherapy (n=501)	Placebo plus chemotherapy (n=496)
EORTC QLQ-C30 GHS/QoL	Number of patients		
	Worsened, n (%)	121 (24.2)	144 (29.0)
	Censored, n (%)	380 (75.8)	352 (71.0)
	Median time to deterioration, months (95% CI)*	NR (36.0, NE)	38.0 (26.7, NE)
	Stratified HR (95% CI)†	0.77 (0.60, 0.98)	
	Stratified log-rank test *P*-value†,‡	0.0168	
Physical functioning	Number of patients		
	Worsened, n (%)	124 (24.8)	151 (30.4)
	Censored, n (%)	377 (75.2)	345 (69.6)
	Median time to deterioration, months (95% CI)*	NR (30.4, NE)	37.7 (16.6, NE)
	Stratified HR (95% CI)†	0.72 (0.57, 0.92)	
	Stratified log-rank test *P*-value†,‡	0.0036	
Fatigue	Number of patients		
	Worsened, n (%)	193 (38.5)	209 (42.1)
	Censored, n (%)	308 (61.5)	287 (57.9)
	Median time to deterioration, months (95% CI)*	16.9 (9.8, NE)	9.4 (5.4, 17.8)
	Stratified HR (95% CI)†	0.83 (0.68, 1.01)	
	Stratified log-rank test *P*-value†,‡	0.0310	
EORTC QLQ-STO22 Symptom index	Number of patients		
	Worsened, n (%)	50 (10.0)	72 (14.5)
	Censored, n (%)	451 (90.0)	424 (85.5)
	Median time to deterioration, months (95% CI)*	NR (NE, NE)	NR (NE, NE)
	Stratified HR (95% CI)†	0.64 (0.45, 0.92)	
	Stratified log-rank test *P*-value†,‡	0.0080	
Dysphagia/ odynophagia	Number of patients		
	Worsened, n (%)	48 (9.6)	54 (10.9)
	Censored, n (%)	453 (90.4)	442 (89.1)
	Median time to deterioration, months (95% CI)*	NR (NE, NE)	NR (NE, NE)
	Stratified HR (95% CI)†	0.81 (0.54, 1.19)	
	Stratified log-rank test *P*-value†,‡	0.1387	
Pain/discomfort	Number of patients		
	Worsened, n (%)	110 (22.0)	134 (27.0)
	Censored, n (%)	391 (78.0)	362 (73.0)
	Median time to deterioration, months (95% CI)*	NR (28.3, NE)	42.2 (33.1, NE)
	Stratified HR (95% CI)†	0.74 (0.58, 0.96)	
	Stratified log-rank test *P*-value†,‡	0.0109	
Upper gastrointestinal symptoms	Number of patients		
	Worsened, n (%)	101 (20.2)	127 (25.6)
	Censored, n (%)	400 (79.8)	369 (74.4)
	Median time to deterioration, months (95% CI)*	NR (NE, NE)	NR (NE, NE)
	Stratified HR (95% CI)†	0.73 (0.56, 0.95)	
	Stratified log-rank test *P*-value†,‡	0.0085	
Dietary restrictions	Number of patients		
	Worsened, n (%)	100 (20.0)	99 (20.0)
	Censored, n (%)	401 (80.0)	397 (80.0)
	Median time to deterioration, months (95% CI)*	NR (40.3, NE)	NR (NE, NE)
	Stratified HR (95% CI)†	0.96 (0.73, 1.27)	
	Stratified log-rank test *P*-value†,‡	0.3936	

Percentages were based on n.
*Estimates are based on Kaplan-Meier method.
†Stratified by regions (east Asia versus ROW [rest of the world]), PD-L1 expression and presence of peritoneal metastasis.
‡One-sided *P*-value was estimated from stratified log-rank test.
CI, confidence interval; EORTC, European Organisation for Research and Treatment of Cancer; GHS/QoL, global health status/quality of life; HR, hazard ratio; NE, not estimable; NR, not reached; PD-L1, programmed death-ligand 1; QLQ-C30, Quality of Life Questionnaire – Core 30; QLQ-STO22, Quality of Life Questionnaire – Gastric Cancer Module.

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